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Medical Research Involving Children – Giving Weight to Children's Views

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Abstract

The quality of health care for children depends much on the availability of relevant results from medical research with children as subjects. Yet, because of their vulnerability and assumed incompetence to take part in decision-making, children have often been excluded from taking part in medical research, so as to prevent them from harm. Empirical data on children's competence to consent to such research used to be rare, but recent developments in this field have created more insights in the myths and realities concerning minor patients' capacities to decide on medical research participation. Against the background of relevant international, European and domestic legal frameworks concerning the rights of children as participants in medical research, this article goes into instruments such as MacCAT-CR, a semi-structured interview format useable as a competence assessment tool for clinical research involving children. On the basis of this, several recommendations are defined to enhance such research, as these may do sufficient justice to the health interests and the capacities of children, while at the same time supporting researchers and child research participants when facing decisions about pediatric research options.

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Keywords

medical research involving children – pediatric research – research participation – children's competence – child decision making – competence assessment tool/ MacCAT-CR – children's views

Introduction

Due to their vulnerability and assumed incompetence to take part in decision-making, children have often been excluded from participation in medical research, so as to protect their well-being. In addition to this, pharmaceutical companies have been reluctant to invest in scientific studies involving infants and children, as the profits of such research have been deemed to be small or even non-existing. These problems have led to a lack of significant research data on the effects of medicinal drugs in children which, inadvertently, places sick children in jeopardy.

Until recently, there were no significant empirical data on children's competence to consent to clinical research. In daily pediatric practice, minor patients' competence to consent is usually assessed implicitly, due to the assumption that a child's ability to understand medical issues is limited. Up to now, the reliability of unstructured competence assessments has been inconsistent, because clinicians possibly did not know which standard to apply (Appelbaum, 2007), while they rendered age standards, prescribed by law, as the guiding principle in their assessments. Furthermore clinicians tend to judge a child competent if the child's decision complies with their own considerations as to what is in the child's best interest (de Vries *et al.*, 2010). Generally, the accepted standard for assessing competence to make medical decisions consists of an unstructured judgment by an expert, trained in the four criteria that reflect the standards to be weighed in most jurisdictions: understanding, reasoning, appreciation, and expressing a choice (de Vries *et al.*, 2010). It follows that more understanding is needed of the issues relating to children's competence to consent in medical decision making as well as how to weigh children's views in this respect. This uncertainty in practice has meant that in the research context as well, the issue of how to "weigh" children has been equally unclear.

The aim of this article is to substantiate a number of recommendations to enhance medical research involving children. These recommendations are believed to do sufficient justice to the health interests and the capacities of

children, while at the same time they may provide support to researchers and child research participants when facing decisions about clinical research options. For reasons of clarity, we distinguish between two meanings of "competence". In legal terms, competence usually refers to decisional skills required under the law or determined by a court. Yet, in clinical practice it is generally addressed as an actual decision-making capacity. In the context of this article, competence – unless mentioned otherwise – concerns the clinically perceptible ability of a person to consent to medical interventions or clinical research. Children's competence to give such consent may not be the same as the respective competence of adults. In cases where domestic legislation demands the application of a fixed age-limit for presumed legal competence, it is necessary that such a limit broadly coincides with children's mental developmental stages. In an ideal situation, statutory age-limits should endeavour to realise an accountable balance between norm and practice. This means that it both warrants protection of involved children's interests in case minors are not fully able to do so themselves; and that this balance should safeguard respect for child autonomy when a child is able to exercise self-determination. Still, health care professionals as well as pediatric patients and their parents would clearly benefit from an available and reliable standard for assessing child competence.

After an overview of the fundamental rights of the minor participant of medical research in view of international law requirements, the Dutch domestic legal framework – which arguably complies with international accepted normative standards – is presented as a general point of reference. Subsequently, the currently most efficient practices for assessing children's competence to consent in pediatric research and the specific factors affecting this competence are investigated. While taking into account that recruiting children for clinical research remains difficult, it will be considered that much can be learned from children's views on research participation, and that this would improve pediatric research practice. A final reflection considers how empirical knowledge on children's rights, views and competences can boost clinical practice and policy-making in view of children's trial participation. This article concludes with several recommendations relating to how to give weight to a child's views on medical research.

1 Medical Research Involving Children: Basic Notions

Medical research involving human subjects below the age of 18 is conducted for various purposes and includes scientific investigations to evaluate the

safety or efficacy of a new drug in comparison to a current medicinal treatment, to monitor the use of diagnostic technologies, to acquire insights in to the quality of life accompanied by a particular therapy or to value the experiences of experts with the application of a new medical device. To clarify certain aspects of such investigations, some basic notions need to be explained.

Foremost, there are different types or categories of medical research. Some research has a mere observational character. In such research the conditions for the test persons are not altered. Instead, bodily, mental or behavioural processes shown by the test persons are closely observed and monitored and then analysed. Another kind of medical research involves actual physical interventions, such as administering study medication or a placebo, undergoing a stem cell transplantation or a new type of operation. Such research is considered to be intervention research and incorporates the implementation of actual physical burdens to the test person. Furthermore, medical research can be therapeutic to the test person. This means that in view of one's state of health the test person is reasonably expected to benefit from trial participation. Non-therapeutic medical research signifies that no particular medical gain is expected to result from participating in the trial. A special category of medical research is non-therapeutic intervention research. Such research is considered not to be of benefit to the test person involved, while it means to undergo activities involving certain risks and burdens for the trial participants. Such research is subjected to strict conditions and demands, especially if it is to be carried out on children, as they are particularly vulnerable and often dependent on others. A central issue in this regard is the permissible amount of risks and burdens to the child when subjected to non-therapeutic trial interventions (WHO, 2005; Ross, 2006).

The normative framework for establishing the permissibility of medical research involving children is strict, as it results from the view that a child's interest in good medical care cannot outweigh the rights of children who participate in medical trials. Critical medical observers, however, believe that this strict framework, despite its valid moral assumptions, also obstructs the necessary advance of pediatric medicine and even has caused medical research involving children to lag behind. Pediatric practice, for instance, shows that various medical remedies for children are not applied on the basis of research with minor participants, but rather on questionable extrapolations of the results of medical research involving adult patients or volunteers. This has resulted in insufficient scientific evidence for the efficacy and safety of particular medical interventions in children, while such care should be adapted to a child's developing physical and mental body. The lack of such adapted care is worrisome, as it leads to sub-optimal medical care for children (Regulation (EC)

No. 1901/2006).[1] Medical practitioners have therefore suggested reconsideration of the conditions for permissible medical research involving children.

Yet, however much the objective of a more child-centered nature of pediatric medicine is to be applauded, the question is how to achieve this goal without eroding the legal protection of children who participate in medical research. If we are to prevent this from happening, one cannot ignore the need for a systematic children's rights approach to medical research involving children.

2 International Frameworks

Article 24 of the UN Convention on the Rights of the Child (CRC) states that children are entitled to enjoy the highest attainable standard of health. Apart from the efforts and measures by States Parties to ensure this standard, the importance of consistent scientific research to enhance the quality of medical care for children is not under discussion. Yet, the permissibility of such research is complex, as the trial participation of children addresses issues such as how to deal with assumed incapacities to give consent or, as already indicated, the maximum level of acceptable risks and burdens for the involved child. The general conditions for permissible medical research are inserted in international ethical and legal documents as well as in regulations of domestic law. In such documents special attention is paid to specific categories of trial participants.

In succession of the ten principles of universally applicable standards for experimentation on human beings, endorsed by the Nuremberg War Criminals Tribunal during the Medical Trial in 1947 and later to be known as the Nuremberg Code (Annas/Grodin, 1992; Shuster, 1997; Freyhofer, 2004), succeeding versions of the World Medical Association's Declaration of Helsinki (Sprumont *et al.*, 2007; Wiesing *et al.*, 2014) identify so-called 'vulnerable groups or individuals', which also include children. Medical research involving these groups or individuals is considered justified only if the research is responsive

1 A European incentive for a breakthrough in this regard is Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for pediatric use and clinical research in vulnerable populations. This Regulation stimulates pharmaceutic companies that aim for a marketing authorisation concerning a new drug, also to draw up a Pediatric Investigation Plan (PIP) containing a research set-up on the use of this new drug in children. A PIP may be omitted if it shows that such research is not necessary (i.e. the involved disease is not current in children). According to Article 36, paragraph 1 of the Regulation, an agreed PIP may lead to a patent extension of six months.

to the health needs or priorities of the group, and the research cannot be carried out without participants of this group. Furthermore, a vulnerable group must benefit from the knowledge, practices or interventions resulting from the research.[2] If the groups are unlikely to derive any health advantages from a trial, a study is only permitted if the burdens or risks of the study interventions are minimal and negligible. In any case, the informed consent of the test person is a key element of accountable medical research involving humans. The International Ethical Guidelines for Biomedical Research of the Council for International Organisations of Medical Sciences (CIOMS) contain similar conditions (www.cioms.ch).

The Universal Declaration on Bioethics and Human Rights of UNESCO (UNESCO, 2005) emphasises – amongst other things – that scientific knowledge, medical practice and associated technologies should be applied and advanced to maximise the benefit for patients, research participants and other affected individuals and that any possible harm to such individuals is to be minimised (Article 4), while also underlining the prior, free, expressed and informed consent of research participants (Article 6). Exceptions to the principle of consent are to be made only in accordance with ethical and legal standards adopted by States, consistent with the principles and provisions set out in the UNESCO Declaration (Article 27) and with international human rights law. The Declaration does not address issues associated with the child as a research participant in particular.

Beyond these ethical research codes, the conditions for permissible medical research on humans are also addressed in instruments of international human rights law. In this regard, Article 7 of the International Covenant on Civil and Political Rights (ICCPR) states – among other things – that no person is to be subjected to medical or scientific experimentation without his free consent. This content of the provision originates from the endeavour of the human community to prevent repetition of the horrific medical experiments preformed on prisoners of war and defenceless inmates of concentration camps by Nazi Germany during World War II (Mitscherlich/Mielke, 1947; Klee, 1997; Weindling, 2004; Weindling, 2015). Although the importance of legitimate consent is beyond dispute, the essential aim of Article 7 is to prohibit experimentations on humans which by nature amount to torture or cruel and inhuman and degrading treatment. This explains why the explicit wording of the ICCPR provision can hardly uphold the view that persons who cannot express their views should be excluded from medical research participation, as in

2 See paragraph 20 of the eighth version of the Declaration of Helsinki, adopted by the 64th WMA General Assembly in Fortaleza, Brazil, October 2013.

effect this would undermine the further development of the quality of medical care for this group of persons (Bossuyt, 1987; CCPR General Comment No. 20, 7; Nowak, 2005). In consequence, proxy consent by accepted representatives to allow these persons' trial participation is generally considered admissible. This means that medical research involving minors, especially very young children, can be acceptable provided their parents or otherwise legal representatives give well-informed consent for their trial participation. In some countries, domestic regulations demand the minor trial participant's explicit approval as well, albeit in consideration of the minor's age and development. We will come to this in more detail in the subsequent paragraphs.

During the genesis of Article 24, CRC, it was debated by the drafting delegations whether this provision on the child's right to health care should also make reference to medical or scientific experimentation or treatment involving children.[3] Despite various viewpoints and suggestions that delegates brought forward – such as the necessity of such a reference, the possibilities for children to consent to trial participation, the information to be provided to children and parents, the child's right to privacy or the doubtful expertise of the drafting delegations to decide about this issue – in the end no conditions for permissible pediatric research were inserted in the CRC provision (Detrick, 1992; LeBlanc, 1995).[4] Although several delegations regretted this outcome, it was noted that the absence of a special paragraph on medical experimentation would not leave children unprotected. In essence, other paragraphs in Article 24, and other CRC provisions more generally, prohibit medical experimentation which is not in the best interests of the child (Van Bueren, 1995; Detrick, 1999). Moreover, this drafting result did not cause the topic to fall into oblivion. In several General Comments, the CRC Committee has addressed the relevance of proper medical research for the benefit of adequate pediatric care and the need to take children's rights into account when such research is prepared and carried out. To be specific: in its General Comment No. 3 (2003, para. 29) on the Rights of Children with HIV/AIDS, the CRC Committee has stressed the importance of children's involvement in decision making regarding their participation in pediatric research; in General Comment No. 12 (2009, para. 103) on the Child's Right to be Heard, the Committee calls upon physicians and health care facilities to provide clear and accessible information to children on their rights concerning their participation in pediatric research and clinical

3 Proposals to that effect were presented by the delegation of Venezuela (E/CN.4/1989/WG.l/WP.21) as well as a special drafting group (E/CN. 4/1989/WG.l/WP.64 in response to E/CN.4/1989/WG.l/WP.46).

4 E/CN.4/ 1989/48, par. 416–431.

trials and to inform them about the research, so that their informed consent can be obtained in addition to other procedural safeguards; in the Committee's General Comment No. 15 (2013, para. 19 and 85) on the Child's Right to Health, researchers are reminded of the fact that the best interests of the child must always prevail over the interest of general society or scientific advancement.

3 European Frameworks

A more precise viewpoint on the subject is to be found in Article 6, para. 3 juncto Article 17, para. 1 section *iv* of the European Convention on Human Rights and Biomedicine (ECHR-Bm). Apart from the general conditions for permissible medical research on humans mentioned in Articles 15 and 16 of this Convention, Article 17 defines particular requirements for therapeutic research involving incompetent persons (para. 1, section *ii*), as well as additional conditions for non-therapeutic research involving such persons (para. 2). Furthermore, the provision indicates the basic characteristics of therapeutic and non-therapeutic research. A therapeutic study involving persons who are legally considered unable to give consent should endeavour to progress scientific understanding of the incompetent subjects' conditions and reasonably produce results of actual and direct benefit for the health of the trial participants. A non-therapeutic trial involving incompetent persons, on the other hand, must aim at a considerate improvement in the scientific understanding of the incompetent subject's conditions. Moreover, it is ultimately to attain results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition. Finally, non-therapeutic research is to entail only minimal risk and minimal burden for the incompetent individual trial participants (Lötjönen, 2005; Radau, 2006).

The ECHR-Bm's Additional Protocol on Biomedical Research underlines, in Article 15, para. 2, section *ii*, the norm of 'only minimal risk and minimal burden' for the incapacitated individual involved in non-therapeutic research, but adds that, '… any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden'. This phrase clearly excludes the possibility to weigh risks and burdens of non-therapeutic research against an assumed potential benefit (Explanatory Report, 2005, para. 90–93; Kandler, 2008). Article 17, para. 1 of this Additional Protocol elaborates that research bears a minimal risk if, having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned.

According to paragraph 2, research bears minimal burden if it is expected to create discomfort that will be, at the most, temporary and very slight for the person concerned. Parents or other persons enjoying the confidence of the child participating in the research are to assess the burden where appropriate (Explanatory Report, 2005, para. 99).

The EU Directive on Clinical Trials on Medicinal Products for Human Use (Regulation (EU) No. 536/2014)[5] – valid as of 16 April 2016 and binding for all EU Member States – also addresses drug research involving children. As a general statement, the Directive's Article 10, para. 1 requires that in a case where a child is a participant to the research, special consideration shall be given to the assessment of the written request to authorise a clinical trial on the basis of pediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of pediatrics. In more specific terms, Article 32, para. 1, section g under *ii* of the EU Directive provides, in addition to the general conditions set out in Article 28, that non-therapeutic drug research involving children may pose only minimal risk to and minimal burden on the minor concerned in comparison with the standard treatment of the minor's condition. This link to the standard treatment puts the criterion of 'only minimal risk and burden' in perspective, especially since Article 32 does not clarify which risks and burdens are acceptable if no standard treatment is available (Guidance Document, 2017). Another issue is how this EU norm relates to the ECHR-Bm and its Additional Protocol on Biomedical Research, now that both European frameworks obviously contain somewhat different norms for non-therapeutic research involving minors. This may lead to undesired variations among European countries as to how which framework will be observed.

As a consequence, at issue is how European States may respond to this ambiguity in European norms on non-therapeutic research involving children with regard to the applicable criterion on risk and burden. Remarkably, the Netherlands has recently amended its current legislation on medical research on humans, while taking due notice of what has been addressed above.

For one thing, the involved statutory modification was preceded by the Dutch government's decision, issued in March 2015, not to ratify the ECHR-Bm (*Parliamentary Papers II* 2014–2015, 34000 XVI, nr. 106). This policy allowed the

5 Originally, this Directive was scheduled to enter into force in October 2018. Yet, the European Medicines Agency (EMA) has decided to postpone the completion of the European web portal and the European database for clinical trials to 2019, due to a delay in the development of the software for the portal and the database. In consequence, the new European legislation on clinical trials will also become effective in 2019: see http://www.ccmo.nl/en/news-archive/completion-eu-clinical-trial-portal-postponed-to-2019.

Dutch legislator to adopt the EU norm in question without being confronted with an incompatibility of binding European standards (Dute, 2015; Buijsen, 2015).[6] As a consequence, Article 3, para. 1, section *d* of the Medical Research Act (MRA; Dutch Bulletin of Acts and Decrees 2016, 424), valid as of March 1st 2017 (Dutch Bulletin of Acts and Decrees 2016, 485) now reflects the implementation of the EU norm for non-therapeutic drug research on children in Dutch law. A new paragraph 2 to Article 3 states that in case no standard treatment is available, the demanded minimal risk and burden of non-therapeutic research on children (and incapacitated subjects) must be related to the nature and severity of the trial participant's disorder (*Parliamentary Papers II*, 2014–2015, 33508, no. 14, pp. 8–9). Additionally, the amendment clarifies that, in view of considerations of regulatory consistency and clarity, this EU-norm also applies to non-therapeutic non-drug research on minors and incapacitated subjects (*Parliamentary Papers II*, 2014–2015, 33508, no. 13, pp. 3–4). Due to the difficulty to generally establish whether non-drug research involves more or less risk and burden than drug research, the Dutch legislator has entrusted this particular issue to the discretion of the authorised Ethical Review Board. This Board is to render judgment on a submitted pediatric research protocol, while taking into account the specific nature of the research's inherent risks and burdens. Through this, a uniform enforcement of the codified norm is believed to be safeguarded (*Parliamentary Papers II*, 2014–2015, 33508, no. 14, pp. 7–8).

In February 2017, the Dutch Central Committee on Research involving Human Subjects, which – amongst other things – reviews non-therapeutic intervention research involving children, has adopted a special assessment framework on such research,[7] in consideration of a recently adopted Guidance Document (2017) of the European Commission Expert Group on Clinical Trials. In this framework, the Central Committee differentiates between acceptable levels of risks and burdens in relation to three different categories of research: non-therapeutic research on healthy child volunteers, non-therapeutic research involving children with disorders, and therapeutic research.

6 This policy decision was inspired by the government's fear that some of the Convention's particular provisions might obstruct relevant advances in medical science and that, in consequence, the amount of Dutch reservations to be made would not allow an accountable ratification of ECHR-Bm. Moreover, present Dutch law was believed actually to include well-considered provisions on medical-ethical issues and these issues, which develop rather dynamically, require, if they are to be considered carefully, room for open-mindedness. Some commentators have criticised the government's decision for being too insensitive to the common responsibility of developing internationally accepted human rights standards.

7 See http://www.ccmo.nl/attachments/files/toetsingskader-onderzoek-met-minderjarige-proefpersonen-versie200117.pdf (only in Dutch).

4 Domestic Frameworks

Obviously, the Dutch regulatory example does not stand alone. Other countries have also established rules on child participation in medical research by national law, particularly in relation to age and consent. In several respects, however, these domestic regulations show mutual differences. A brief overview of some of these differences may illustrate various legal approaches to this issue.

From a general point of view, it is clear that medical research projects, before they are being implemented, require approval by expert bodies, such as ethical committees or institutional/scientific review boards. These bodies are to assess a research protocol on its medical-scientific quality and relevance, pharmacological aspects, methodological validity, ethical and legal accountability, the likelihood of beneficence and the acceptability of levels of involved risks and burdens, not at the least viewed from a research participant's perspective. Apart from mandatory review criteria, it is beyond dispute that due to the principle of decisional autonomy, research participants or their lawful proxies must be adequately informed – in writing as well as orally – about all relevant aspects of a proposed research project, in order to live up to the requirement of informed consent. With regard to children, parents usually have the legal authority to give permission for research participation, while children can provide consent to their involvement in biomedical research when considered appropriate under national law.

However, domestic regulations in Europe show a wide variety as to when a child is considered competent to consent to health care interventions, while regulations hardly clarify how a required competency should be established. In some countries autonomous decision-making is considered lawful only from the age of 18, while other countries recognise a decisional authority in matters of health care from a fixed age below the age of legal majority. In the Netherlands, for instance, parents must give consent if their children of an age below 12 are to participate in a medical research project, whereas this child still must be informed about such project in conformity with its level of understanding. As of age 12 competent minors are legally required, in addition to parental consent, to agree to medical research participation. Besides, researchers must be aware of possible signs of opposition to (continued) research participation of children, especially when they are very young (Code of Resistance, 2001). The information provided to research participants must, in fact, contain references on how such opposition can be established. Furthermore, the recently amended MRA accepts a competent minor's ability to give informed consent to trial participation without parental involvement from the age of 16. This codification

reflects current Dutch legal understanding that in relation to health care matters a child's view is considered to be decisive as of age 16, even though the child has not reached his majority under Dutch civil law, which is as of age 18. In comparison, the Danish Act on Clinical Trials of Medicinal Products[8] requires that research on a person who has attained the age of 15 is permitted only if this child and the custodial parent consent to this (Article 4–1). Danish children between 5 and 15 years of age must, to the extent possible, be consulted about their participation in a clinical trial (Article 4–2).

Under the Swiss Human Research Act[9] no specific age conditions apply with regard to informed consent or assent by minor research participants. Instead, it is mandatory (Articles 22 and 23) that competent children are informed and give consent to their research participation (in therapeutic as well as non-therapeutic research) together with their legal representative. Incompetent children must be incorporated in the consent procedure as much as possible, while the views of incompetent children should be given weight according to their age and maturity (Article 21).

In Germany, there is no federal legislation on medical research involving humans, even though special regulations with regard to medicinal products (Arzneimittelgesetz), medical devices (Medizinproduktegesetz) and radiation (Strahlenschutzverordnung, Röntgenverordnung) contain rules that are considered applicable. Testing medicinal products on children, for instance, is permitted only if it occurs within the framework of clinical studies. Fundamental research involving children in order to test medication is rarely allowed, as this is considered to offer no potential gain to the child participant. Still, in general terms, a child participating in medical research in Germany enjoys a similar legal protection as his Swiss counterpart (Article 40, section 4 Arzneimittelgesetz; Radau, 2006, Sprecher 2007; von Freier, 2009).

The Belgian Act on Medical Experimentation on Humans[10] also demands the informed consent of the child's legal representative, as well as the child's involvement in the consent procedure, provided this complies with his age and level of maturity (Article 7). Moreover, the information a child must receive, should be provided by a pedagogic qualified professional and be adapted to

8 This Act – Lov om kliniske forsøg med lægemidler – was adopted in the Danish parliament on 10 May 2016. See https://laegemiddelstyrelsen.dk/en/about/targets-and-tasks/legislation/the-danish-act-on-clinical-trials-of-medicinal-products/~/media/0BDD2C209E3A472EB4DFC00661683433.ashx.

9 The Swiss Act – Humanforschungsgesetz (Hfg) – is valid as of 1 January 2014. See https://www.admin.ch/opc/de/classified-compilation/20061313/index.html.

10 The Belgian Act – Wet inzake experimenten op de menselijke persoon – is valid as of 1 May 2004. See http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=2004050732&table_name=wet.

the child's degree of understanding. Nevertheless, the Belgian Act makes no reference to specific age conditions that might be relevant in view of recognising autonomous decision-making rights of a child participating in medical research. The same is current in Canada (Canadian Institutes for Health Research *et al.*, 2010).

In the United States of America, it is generally up to parents or legal guardians to give informed permission for medical care of their offspring, while children close to the age of 18 are to give assent, meaning an affirmative agreement (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1977; National Institutes of Health). With respect to medical research, it was observed that even though the American Academy of Pediatrics and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommend assent for children as of age seven, wide variation remains on the inclusion of children in the assent process (Whittle *et al.*, 2004; Katz/Webb, 2016). The ability of the capable, mature child to consent to medical research depends on individual USA state laws, while generally, risks must be minimal and the research aim should be on a medical condition for which the child can legally give consent (Alderson, 2007).

This means, in short, that countries which have adopted a flexible system reflecting that any competent person is permitted to give informed consent, require clinical researchers to examine the child's decisional abilities on a case-by-case basis (Stultiens *et al.*, 2007). Yet, the question is, whether such an approach offers enough safeguards for the required legal protection of a child who is about to take part in medical research. Beyond the level of domestic law, Article 5 juncto Article 6, para. 2, ECHR-Bm as well as Article 14, para. 3, juncto Article 15, para. 1, section *iv* of the ECHR-Bm's Additional Protocol on Biomedical Research, reveal that a minor is to take part in the informed consent procedure in proportion to age and degree of maturity (Kandler, 2008). For that reason, it is all the more important that children are enabled to grasp the pros and cons of medical research participation and that proper notice of their views in this regard is ensured. This also requires facilitating the child's participation rights in relation to its involvement in medical research.

5 Empirical Data on Children's Decision-Making Competence Regarding Research Participation

Having charted the latest developments in children's competence assessment, we record that little progress has been achieved over the last decades. This is partly due to the fact that the debate about children's competence to consent

to medical issues has been concentrated on complex normative concerns. A consensus over a clear operationalisation of children's decision-making competence is far from being reached (Hein *et al.*, 2015 (A)). Consequently, little empirical research has been conducted on competence assessment in children. Therefore, we believe that an empirical research agenda can contribute to initiate advancements. In essence, more research data are needed to examine theories that are brought forward and to review guidelines and specific regulations dealing with children's decision-making competence in a medical care context.

As a starting point, the accuracy of existing tools for assessing competence to consent used in clinical populations has been examined in recent research (Appelbaum/Grisso, 2001). Although many different instruments were described, few were tested in a systematic way. It was found that studies on the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) show clear indications of reliability and validity in adult populations (Appelbaum/Grisso, 2001).

The MacCAT-CR is a semi-structured interview format that helps clinical investigators to assess research candidates' competence to give informed consent to participation in trials. It measures the four aspects of decision-making capability that reflect the standards for competence to consent in most jurisdictions: (1) *understanding* the disclosed information about the nature of the research and its procedures; (2) *reasoning* in the process of deciding about participation, with a focus on abilities to compare alternatives in the light of their consequences; (3) *appreciation* of the effects of research participation (or failure to participate) on their own situation; and (4) *expressing a choice* about participation.

The MacCAT-CR provides a format for disclosing selected information on the research project at hand. A standard set of questions then assesses candidates' abilities to understand the information, reason about it, appreciate its consequences and express a choice. The interview samples their abilities using representative content, rather than testing them on the full content of a typical informed-consent disclosure.

Used alongside the MacArthur Competence Assessment Tool for Treatment (MacCAT-T) (Grisso, 1997) the MacCAT-CR often proved to be the best assessment tool available. In consequence, a research protocol on how to assess children's competence to consent to clinical research by using the MacCAT-CR was drafted. The MacCAT-CR was translated and adjusted to be used in children aged 6 to 18, by including easy language to be understood by elementary school-aged children and additional questions on the influence of

relationships with parents and peers (Hein *et al.*, 2012). The study was conducted by using a sample of 161 pediatric patients who visit inpatient and outpatient clinics of pediatric departments of allergology, gastroenterology, oncology, ophthalmology and pulmonology. Elective clinical research projects included 3 observational studies and 10 randomized clinical trials. Competence judgments by experts aware of the four aforementioned criteria were used to establish the reference standard. The index test was the MacCAT-CR. Validity of the MacCAT-CR outcomes was supported by high overall accuracy in correctly classifying children as competent against the reference standard.

The study showed that children's competence to consent to clinical research can be assessed validly and reliably by using the MacCAT-CR (Hein *et al.*, 2014). In the same study, the four domains (understanding, appreciation, reasoning, and expressing a choice) representing competence in most jurisdictions appeared to constitute a single trait or continuum of competence in children. Hence, a cut-off score on the MacCAT-CR, above which competence was considered likely, could be estimated. The research results suggested that age limits for children who are believed competent to decide on research participation can be estimated, for children of 11.2 years and above generally appeared to be competent, whereas children of 9.6 years and younger were generally not competent. A change-over occurred between 9.6 and 11.2 years, and the cross-over point was estimated at 10.4 years.

Of all factors that were considered to influence children's competence, the key determining factor was age. Intelligence as measured by the Wechsler Nonverbal Intelligence Quotient appeared to be of influence as well. Theory-based assumptions suggesting that risk and complexity of the decision would be related to a competence classification could not be confirmed with empirical data (Hein *et al.*, 2015 (B)). This advocates that for radical decisions that imply a higher level of competence, a matured age is not necessarily required. This may indicate that children of a certain age who are able to make less complex/low risk decisions could possibly also make high complex/high risk decisions at that same age. A possible explanation for this may be that children at a certain age possess the required capacities, and that competent decision-making is probable when the information children receive is of good quality. For other potential determining factors for competence – factors such as gender, the influences of social relationships, disease experience, ethnicity, and socio-economic status – shown by previous studies, no significant connection with competence could be demonstrated. Still, an interesting observation was the tendency of parents to consider their child more readily competent than experts did.

6 Children's Views on Participating in Medical Research

As already mentioned, we believe there is a compelling need for more pediatric drug trials, since it is clear that an alarming percentage of medication (36–90 per cent) prescribed to children has not been tested in the respective age group (Cuzzolin *et al.*, 2006). Although adapted pediatric research guidelines and applicable domestic regulations warrant minor trial participant's safety, doing research in children is still bothered by unsatisfying trial recruitment of children. For this reason a literature review on potential determining factors for children's participation or non-participation in clinical research was conducted. This review of previous studies revealed – amongst other things – that providing child participants with inadequate information about the particularities of a trial also interferes with the participants' ability to make well-considered decisions (Hein *et al.*, 2015 (C)). Studies in adolescents, one of which concerned a hypothetical research project, showed that several participants expected direct health benefit from being questioned and examined by the physician, that a main reason for trial participation was altruism, and that half of the eligible trial subjects decided not to participate for no discernible reason. In addition, sample sizes of the studies were small, children under 12 were underrepresented and studies did not provide relevant results for subdivisions of children in different age groups (Hein *et al.*, 2015 (C)).

A recent study included a qualitative and quantitative analysis of reasons why participation rates of children in clinical research are problematic. The researchers explored qualitatively children's views on research participation across different age spans. In a sample of 35 pediatric patients eligible for clinical research participation in the age of 8 to 16 years, semi-structured interviews were dedicated to children's thoughts on research participation. Children were asked questions, such as: what would you rather do, participate or not?; why would you rather participate, or not participate?; what do you think is good about participating and what is not good about it?; why would you prefer participating (or not participating) above not participating (or participating)?' The ages of the study's sample ranged from 8–16, with an average of 11.9 years, SD 2.45. In this sample 25 children (71 per cent) decided to participate in the presented clinical research. The qualitative study on reasons that promote or discourage research participation expressed by children of different ages demonstrated that time constraints and direct burdens from the research procedures, such as waiting, sitting still, or extra tests, were the main reasons for not participating for children of 9 years and older. Research procedures that were considered burdensome to children varied between individuals. The sample included no trial procedures that required extra vena punctures or lumbar

punctures, but concerned procedures such as electroencephalography, electrocardiography, magnetic resonance imaging, extra medication, diaries, and anorectal manometry. In general, children older than nine years were able to convey clearly their assessment on burdens and benefits.

Altruism appeared to be a main reason for children of ten years and older to participate in medical research. This corresponds with findings in the adult population (Townsend/Cox, 2013). Another important motive for trial participation was that children mistook research for individual treatment and expected health gain from being a trial subject. This therapeutic misconception was prevalent in the population of children under 13, but not in late adolescents. In adults, therapeutic misconception emerged as a major theme (Townsend/Cox, 2013), in previous studies in children it was prevalent as well. All this shows that children's understanding of the purpose of clinical research relies heavily on the provision of information, which should be tailored to their comprehension level. Although children in this sample were well-informed about the purpose of the research, including an explanation of the difference between therapeutic goals and research goals, younger children and early adolescents showed difficulties in understanding this.

As the majority of children older than nine years were able to convey their assessment on burdens and benefits in a clear way, it might be worth considering giving children greater voice in assessing what they experience as burdensome and valuable in research. A proper example in this regard is provided by the Young Person's Advisory Board of the UK Medicines for Children Research Network.[11] This Board – which consists of children, aged 8 to 18 years, who have experienced medical conditions – involves children and their families in research and raises research awareness and motivation amongst young people. Expanding similar initiatives may contribute to improving the quality of pediatric research recruitment.

7 Recommendations

Seen from a children's rights perspective, the importance of consistent scientific research to enhance the quality of medical care for children is undisputed. It is, therefore, for good reason that the CRC Committee's General Comment No. 12 (2009, para. 103) addresses this dimension of child health care. Still, the permissibility of such research is complicated, as trial participation of

11 See, http://www.crn.nihr.ac.uk/children/pcpie/young-persons-advisory-group/.

children touches upon issues such as how to deal with their assumed incapacity to give consent or which level of risks and burdens is acceptable for the involved child.

Ideally, statutory age limits for alleged competence in children aim to strike a balance between protecting children's interests when they are not fully able to take care of this themselves and to respect their autonomy when they are able to do so. If a fixed age limit for alleged competence in children is used, such a limit should generally be in accordance with a child's developmental stages. Earlier studies (Hein *et al.*, 2015 (D)) offer an empirical fundament for setting a reasonable and just age limit. Until now, there is enough evidence which suggests that the age limit which most validly reflects children's competence is 11 or 12 years. An alternative for the fixed age limit is a case-by-case assessment of decision-making competence. Research data advocate that unstructured performance of competence assessments is often sub-optimal. Consequently, the reliability of unstructured judgments has been poor. To avoid this bias, a case-by-case assessment would require an objective assessment rather than the currently used intuitive one. Arguably, the MacCAT-CR delivers a useful instrument for this purpose in the pediatric research context to be used in competence assessment.

Even before children have reached a level of decision-making competence that legally allows them to have a say in the informed consent procedure, their involvement in health care procedures should be pursued. Investigating children's views on medical trial participation has shown that children from the age of nine are able to convey their views on burdens and benefits in a clear way, whereas children below this age can still be engaged in the medical care process if tailored to their level of development. Children have shown to assess particular issues like their level of understanding of research related aspects, whether the information provision for parents and young children is satisfactory and which logistic burdens may (negatively) influence their willingness to participate in research. Therefore, strategies concerning children's involvement in medical research procedures should aim to improve these issues. To that effect, several recommendations may be considered.

A starting point for these recommendations can be found in the Report of the Doek Committee (2009), containing an advice to the Dutch Minister of Health Care regarding the legal position of children as participant of pediatric research, while exploring the possibilities to increase the options for such research under Dutch law. Leaving from the basic principles of the CRC the Doek Committee stressed that in a clinical research context a child is not just to be regarded as an object of care and protection. An essential consequence of the CRC is that this child is explicitly recognised as a subject of rights; rights,

which a child must be enabled to enjoy in accordance with his or her evolving capacities. Relevant in this regard is that a child should have opportunities to form his or her own views and to express freely these views, also in relation to medical research involving minor subjects, whereas it is imperative to take due notice of these views in accordance with the child's age and maturity. Article 12 CRC constitutes a crucial element in a research practice which targets proper information to and active participation of children in decision-making processes. This goes for decisions regarding medical treatment and medical research as well (Report of the Doek Committee, 2009). Arguably, the Doek Committee's point of view is also in line with the CRC Committee's remarks on this matter reflected in its General Comment No. 12 (2009, para. 103).

These very observations can support the recommendation that children should not just be approached when research is to be carried out, but even when research designs are being considered or drawn up. This could offer possibilities for researchers first to adapt a foreseeable level of risks and burdens to what children might view as acceptable, thus increasing the chances of meeting the desired amount of participant inclusions when a study is implemented (General Comment No. 3, 2003, para. 29). Logistic burdens, for instance, should be minimised by coaching and guiding children and parents and by considering the accessibility of research facilities. Involving children and parents in advisory boards is a way to improve research awareness among eligible research participants and further to align research procedures with young trial participants' preferences. In this respect, it can be asserted to stimulate the membership of minors in ethical review committees, since these committees assess the quality and feasibility of pediatric research proposals. Although the Dutch statutory system of ethical review already requires a layperson's membership of such committees, all committee members are adults. Safeguards for an authentic children's view on pediatric research proposals within the context of ethical review of pediatric research may therefore be welcomed.

As the CRC Committee has stressed in General Comment No. 12 (2009, para. 104), States Parties are to introduce measures enabling children to contribute their views and experiences to the planning and programming of services for their health and development. Their views are to be sought on all aspects of health provision, including what services are needed, how and where they are best provided, discriminatory barriers to accessing services, quality and attitudes of health professionals, and how to promote children's capacities to take increasing levels of responsibility for their own health and development. Salutary in this respect could be the application of feedback systems for children who are involved in research and who take part in consultative processes. The gain of all this may be transmitted to local or national children's

councils, e.g. child councils in hospitals,[12] and ultimately to parliaments, so as to develop standards and indicators of health services that respect the rights of the child. This would better ensure that children's own wishes – as groups and individuals – are more effectively weighed in questions of whether they should participate in medical research.

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12 Note the institutionalised child councils (Kinderadviesraden, KAR) established in several Dutch children's hospitals. These councils, composed of child patients, are in contact with hospital boards to discuss – amongst other things – what aspects of child health care may be improved. Issues of consideration are, for instance, how paediatricians communicate with child patients, if a child-friendly atmosphere is preserved and necessary facilities (internet/Wifi) in long-stay rooms for ill children are being maintained, whether care personnel is nice or if the food for child patients is satisfactory. The councils not only address what they consider to be improvable, they also provide suggestions as to how improvements might be realised. These councils tend to have their own website (in Dutch) as well. See, http://www.amaliakinderziekenhuis.nl/over-ons/kinderadviesraad/; https://www.jeroenboschziekenhuis.nl/Publicaties/125522/Over-JBZ-Organisatie-Raad-van-Kinderen; https://www.ysl.nl/patient-en-bezoeker/uw-ervaring-of-klacht/clientenraad/kinderadviesraad/; https://www.umcg.nl/NL/Zorg/Kinderen/kar/Paginas/default.aspx; http://jongeren.julianakinderziekenhuis.nl/over-juliana-kinderziekenhuis/wil-je-met-ons-meedenken/kinderadviesraad-(kar).aspx.

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